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Redefining Normal Low-Density Lipoprotein Cholesterol

A Strategy to Unseat Coronary Disease as the Nation's Leading Killer

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The new Adult Treatment Panel guidelines will be published in 2011. This paper suggests the consideration of major changes in the existing management guidelines for low-density lipoprotein cholesterol management based on 2 fundamental principles: return the low-density lipoprotein cholesterol level to the normal range and begin treatment closer to disease onset. These principles suggest the value of rethinking all 3 of the principal features of the Adult Treatment Panel III guidelines for low-density lipoprotein cholesterol management: the initiation criteria, the use of variable targets, and the level of the treatment target. Because the principal issue surrounding guideline change is likely to be uncertainty concerning cost and toxicity, the text of new guidelines would have to completely satisfy this concern by strong emphasis on a prudent conservative approach to implementation and would include both cautionary data and caveats concerning the tradeoffs between the potency, cost, and toxicity of statins. The proposed changes in the guidelines, if combined with effective implementation, would likely lead to the displacement of atherosclerotic disease as the nation's number 1 killer. This review provides a logical rationale and discusses the pros and cons for each of the proposed changes. (J Am Coll Cardiol 2010;56:630–6) © 2010 by the American College of Cardiology Foundation

Sometime in 2011, a group of experts in lipidology will finalize a set of recommendations that will alter the preventive management of coronary heart disease for the next decade. These new Adult Treatment Panel (ATP) guidelines will be among the most important in all of medicine for 2 reasons. They will deal with the leading cause of morbidity and mortality in the Western world. They will be endorsed by the U.S. Food and Drug Administration, and millions of health care practitioners worldwide will implement the recommendations. Ironically, any proposed change to the guidelines cannot be free of controversy because these particular guidelines, unlike many in cardiology, cannot be based on rigorous medical science. Instead, like the existing ATP III guidelines, they will have to find the practical middle ground between scientific proof and logical inference. This review proposes a logical rationale for 3 major changes in the existing management guidelines for low-density lipoprotein cholesterol (LDL-C) that, combined with effective implementation, would lead to displacement of atherosclerotic disease as the nation's number 1 killer.

If the new recommendations are to dislodge coronary atherosclerotic disease as the leading cause of death, we might begin with the logical question: Is there an LDL-C level at which recurrent coronary events are effectively arrested and/or new atheroma do not develop? Although it is tempting to term this the normal level of LDL-C, we cannot say that it would be devoid of long-term adverse outcomes, so a more precise and descriptive term may be the putative normal LDL-C level.

The Asymptomatic Population as a Putative Normal

The earliest approach to defining a normal level of LDL-C was traditional: determine its Gaussian distribution in a clinically asymptomatic population. At that time, the calculated median LDL-C level was approximately 130 mg/dl (1). In the existing ATP III guidelines, this value appears as both the level for initiating therapy in patients with disease and as a therapeutic target for those without known disease. In population studies, however, 35% of patients with myocardial infarction are asymptomatic before the event, so a normal population cannot be defined by the absence of symptoms. Further, in statin trials, only 25% to 35% of events are prevented as LDL-C is reduced to 100 to 130 mg/dl, independent of the presence or absence of symptoms. We may infer that clinical presentation cannot be used to establish a putative normal LDL-C level and that the 130 mg/dl cut point has little support in the recent published literature.

Defining Putative Normal From Nonatherosclerotic Populations

An alternative approach was suggested 5 years ago by O'Keefe et al. (2). Beginning with the total cholesterol level

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of 80 to 110 mg/dl in nonatherosclerotic wild mammalian species, they calculated the LDL-C level to be approximately 35 to 70 mg/dl (Fig. 1). Humans are born with LDL-C levels in this range, but the level gradually increases with age. At least 2 adult human populations, however, do not exhibit this progressive increase in LDL-C with age. One population consists of hunter-gatherer societies, diverse in geographic location and ethnic origin but arguably living the way humans did 10,000 years ago. LDL-C levels remain in the 35 to 70 mg/dl range. In modern societies, rural Chinese blood levels often fall within this range. In neonates and these 2 adult groups, atherosclerotic coronary disease is rare. The consistency of these diverse human data sources, taken together with the mammalian species data, supports the speculation that the putative normal range of LDL-C in adult humans may be approximately 35 to 70 mg/dl.

Testing a Putative Normal Range of LDL-C in Humans

Two recent randomized clinical trials allow the next logical step: examining the effect of therapeutic LDL-C lowering into this putative normal range. In ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound), reduction of LDL-C from 130 mg/dl to 61 mg/dl (12% <40 mg/dl LDL-C and 41% between 40 and 60 mg/dl) resulted in regression of carotid atherosclerosis (3). In JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), reduction of LDL-C from 108 mg/dl to 55 mg/dl in an asymptomatic intermediate-risk population resulted in a 44% reduction in adverse cardiac events to 1.4% in those with on-treatment LDL-C <70 mg/dl (4). Neither trial identified increased statin-induced toxicity at lower on-treatment LDL-C levels.

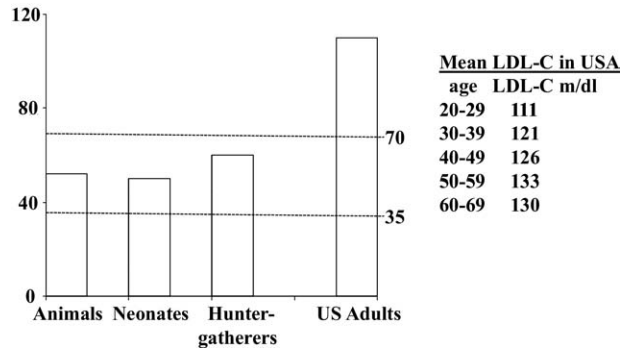

Figure 1 The Level of LDL-C in Different Species and Populations

The level of calculated low-density lipoprotein cholesterol (LDL-C) levels in wild animals (baboon, monkey, horse, bear, rhinoceros, elephant, wild pig), neonatal humans, and hunter-gatherer societies is in the range of 35 to 70 mg/dl (2). The mean LDL-C level in U.S. adults is approximately twice this value. Because humans are the only animal species in this range (excluding some animals domesticated for human consumption), a reasonable question is whether the putative normal LDL-C for all mammals is in the 35 to 70 mg/dl range.

Abbreviations and Acronyms

ATP = Adult Treatment Panel

LDL-C = low-density lipoprotein cholesterol

These new data are supported by linear extrapolation of on-treatment LDL-C levels in both secondary angiographic and primary prevention trials. In the former, lesion progression reaches zero at an LDL-C of 67 mg/dl and coronary events reach zero at approximately 30 mg/dl (2). In primary prevention trials, major adverse cardiac events reach zero at an on-treatment LDL-C level of 57 mg/dl. Thus, to the lipid profiles in mammals, neonatal humans, and isolated human societies, we may add clinical trials that suggest the putative normal LDL-C level may be approximately 35 to 70 mg/dl.

Insights Derived From New Lifetime Follow-Up Data

As LDL-C levels rise above the putative normal range, atherosclerosis begins to appear. At ages 12 to 17 years, LDL-C reaches 87 mg/dl, with approximately 5% to 7% of this group already at a level >130 mg/dl (5). The monotonic progression of coronary atherosclerosis with decades of age has been documented by intracoronary ultrasound imaging of donor hearts at the time of transplantation (6) (Fig. 2). Plaques of at least 0.5 mm were found in 17% of 13 to 19 year olds and increased to 60% in 30 to 39 year olds. The presence of these ultrasound-identified plaques predicts long-term morbidity and mortality at follow-up (7).

Of critical importance to the new guidelines, those at risk of developing atherosclerosis can be identified in youth. In the Bogalusa Heart Study, autopsy of young adults who had a previous risk factor analysis show those with ≥3 childhood risk factors had a 9-fold increase in atherosclerotic plaque area compared with those with none (8). Lipid abnormalities in childhood also predict early onset of clinical disease. For instance, in adults with onset of cardiovascular disease between ages 39 and 45 years, their childhood mean triglyceride level of 127 mg/dl and body mass index of 24 kg/m^2 contrasted to those without clinical disease with a triglyceride level of 72 mg/dl and a body mass index of 20 (9). Finally, LDL-C lowering during early atheroma development induces regression. In children with familial hypercholesterolemia, pravastatin 20 to 40 mg/day for 2 years induced a 24% reduction in LDL-C, accompanied by a significant reduction in carotid intima-media thickness compared with both baseline and placebo controls, with no difference in growth, muscle, or liver enzymes or in endocrine function (10). We may conclude that atherosclerotic disease begins in youth, that the risk of the development of clinical disease can be identified decades before its clinical presentation, and that the disease can be arrested or reversed during this period.

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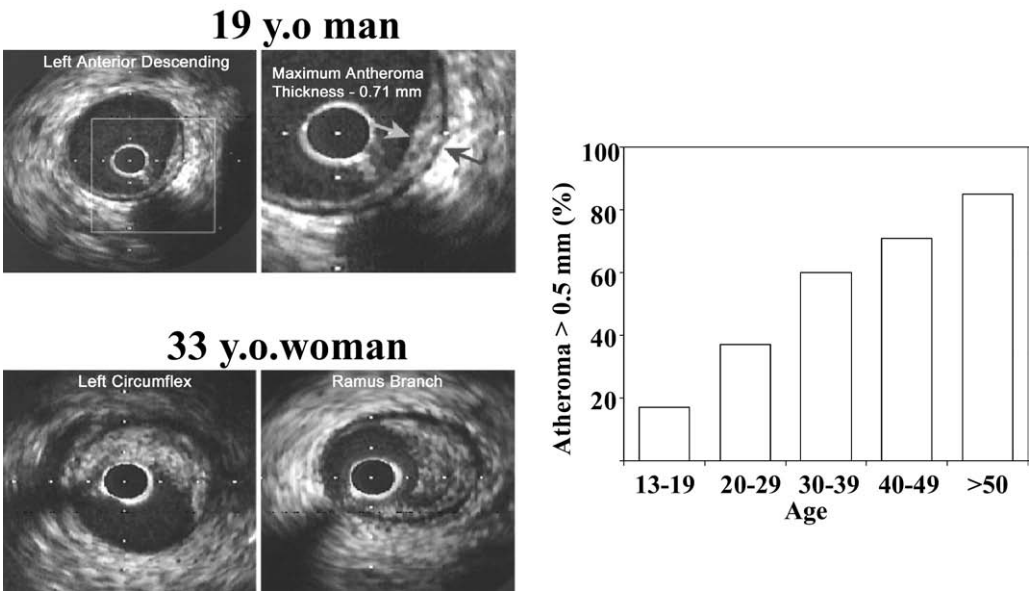

Figure 2 Coronary Atherosclerosis in Young Adults

Intravascular ultrasound imaging in 262 heart transplant recipients at 2,014 sites within 1,477 segments in 574 coronary arteries. Lesions with an intima thickness >0.5 mm were defined as atherosclerotic. In this population, 52% had lesions, ranging from 17% in individuals younger than 20 years to 85% in those older than 50 years of age. In those with lesions, intima thickness averaged 1.1 mm and area stenosis was 33%. Data taken from a large number of age-stratified autopsy studies establish the fact that coronary atherosclerosis begins in youth. If many of these individuals are those destined to become those who compose the >50% mortality statistic, therapeutic lowering of the LDC-C to the putative normal range might logically begin during this point in pathogenesis, provided that they can be accurately identified. Images are reproduced with permission and figure is adapted from Tuzcu et al. (6).

Implications for Recommendations and Guidelines

In guideline jargon, the level of evidence of the putative normal LDL-C level is clearly C, supported only by inference from existing data, as are the current guidelines. A further daunting issue is that if atherosclerotic disease begins in youth, then the duration of disease vastly exceeds the duration of randomized trials of lipid-lowering therapy used to support guideline development. From first principles, a 2- to 5-year trial cannot be assumed to predict either efficacy or toxicity over 40 to 60 years of therapy with scientific rigor. The remarkable implication is that, unlike other guidelines, those for LDL-C now and for the foreseeable future will be based on inference (Table 1). At a minimum, however, guidelines need basic principles that serve as their foundation. The putative normal range of LDL-C and the appearance of disease as blood levels exceed this range suggest 2 fundamental principles: return the LDI-C level to the normal range and begin treatment closer to disease onset. The role of guidelines is then to translate these principles in a manner that maximizes the relationship between efficacy and risk at reasonable cost. In this context, the putative normal LDL-C level, the origin of atherosclerosis in youth, and the availability of low-cost potent statins suggest the value of rethinking all 3 of the principal features of ATP III guidelines for LDL-C management: the initiation criteria, the use of variable targets, and the level of the treatment target.

Rethinking Initiation Criteria

The ATP III initiation levels incorporate 2 fundamental problems. First, they now seem far too high (e.g., 190 mg/dl for Framingham low-risk individuals and 130 to 160 mg/dl for asymptomatic individuals with risk factors). As 1 example, in the asymptomatic JUPITER population with a mean LDL-C level of 108 mg/dl, approximately one-half of the

Table 1 Proof Versus Inference: Why Coronary Artery Disease Requires a Different Mindset

• Humans are the only free-living animal in which atherosclerosis develops, so animal research cannot define natural history.
• The traditional use of apparently normal individuals to establish a normal range cannot be used for LDL-C.
• The duration of the disease vastly exceeds the duration of randomized clinical trials.
• The efficacy results of 2- to 5-year randomized trials cannot predict the efficacy of 40 to 60 years of therapy.
• Acute toxicity results of trials are made grossly misleading by the 1-month run-in period before randomization.
• Short-term absence of toxicity cannot be taken to predict long-term absence of toxicity.
• As a consequence, guidelines for LDL-C management must be based on logical inference rather than scientific rigor.

LDL-C = low-density lipoprotein cholesterol.

patients had a calculated 10-year risk Framingham risk level <10% (4). Nonetheless, there was a 44% reduction in events when LDL-C was reduced to the middle of the putative normal range. Second, an even more serious problem involves calculating risk based on the 10-year probability of a cardiac event. The risk calculation is very heavily weighted by age, such that the calculated mean 10-year risk for 25-year-old men increases 7-fold over 30 years (Fig. 3) (11). Younger individuals with a high risk factor burden clearly have a high probability of atherosclerotic disease, but have a low calculated 10-year risk and thus do not become candidates for treatment until the disease is very well established. For asymptomatic individuals, the magnitude of the limitation inherent in use of the 10-year risk rather than disease pathogenesis as the initiation criterion is substantial: approximately one-half of those in whom coronary artery disease develops first present with either sudden death or acute infarction.

Reorienting the initiation criteria toward the pathogenesis of atherosclerosis rather than its first clinical manifestation is actually eminently feasible. Data to support at least 3 methods are currently available. An individual's risk can be expressed relative to the average risk for that person's age. Alternatively, the individual's calculated risk can be expressed relative to optimal values. Finally, a third approach with the same philosophy is to calculate the Framingham risk over 30 years rather than the current 10-year period (11). Each of these methods is amenable to creation of simple objective initiation criteria. As an example, a young individual with risk in the upper 10% of that age group, or a calculated 2- to 3-fold greater risk than optimum, or a 40% 30-year risk might be identified as a candidate for pharmacologic therapy. Independent of which methodology is chosen, to dislodge atherosclerotic disease from its number 1 position, it seems essential that the new guidelines incorporate the logical concept that a long-term disease requires a long-term solution (i.e., that management begin earlier in the course of the disease).

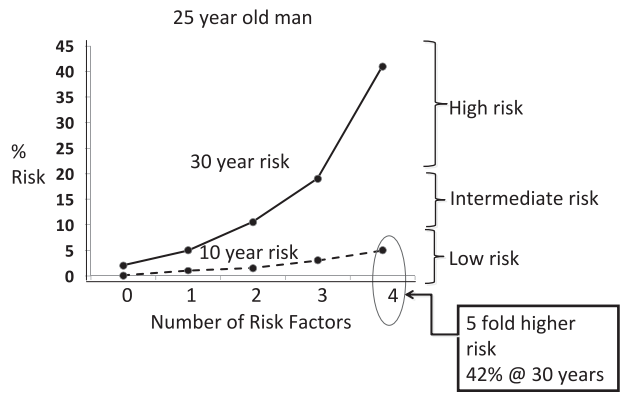

Figure 3 **Risk Factors and Coronary Atherosclerosis in Youth**

The critical flaw in the use of the 10-year risk of a coronary event as an initiation criterion. An example of the approximate 10- and 30-year Framingham risk of coronary heart disease for a 25-year-old man with or without clinical risk factors (total cholesterol 150 mg/dl vs. 260 mg/dl; high-density lipoprotein cholesterol 35 mg/dl vs. 60 mg/dl; systolic blood pressure 110 mm Hg vs. 160 mm Hg), smoking, and diabetes. A young man with 4 risk factors is at low 10-year risk (<5%) whereas his risk of a cardiac event before age 55 years exceeds 40%, and his risk is 5-fold greater than a man with no risk factors. The arbitrary choice of 10-year risk of a coronary event needs to be replaced with a method reflecting the pathogenesis of coronary artery disease, which begins in young adults. This concept is incorporated in both the absolute 30-year risk and in the individual's relative risk within his/her age group. Adapted, with permission, from Pencina et al. (11).

Rethinking the LDL-C Target

A logical LDL-C target for individuals selected for therapy is the putative normal range, with the proviso that it can be achieved at acceptable cost in the absence of toxicity and that neither patient nor health care provider use drug therapy as a substitute for lifestyle modification. Indeed, a naturally or lifestyle-induced low LDL-C is not necessarily the same as medication-induced low LDL-C. The alleged efficacy of LDL-C lowering is derived predominantly from 5-year clinical trials, whereas the magnitude of benefit derived from an earlier and sustained lifetime of lower LDL-C is poorly defined. An experiment of nature provides potential insight. In the ARIC (Atherosclerosis Risk in Communities) study of a free-living population, approximately 3% have sequence variants in the gene colloquially called *PCSK-9* (pro-protein convertase subtilisin/kexin type 9 serine protease). These variants lower LDL-C by a mean of approximately 19% compared with the general population. Individuals with the *PCSK* mutation have had a mean 62% lower rate of cardiac events over the first 15 years of observation (Fig. 4) (12). These data suggest that the efficacy of a lifetime of lower LDL-C level and the inference that if therapeutic lowering of LDL-C had a similar long-term impact in higher risk asymptomatic younger individuals, well-constructed guidelines could result in a major reduction in cardiac events. Thus, pathologic, epidemiologic, and clinical trial data suggest that a single putative normal LDL-C target might reasonably replace existing arbitrary multiple targets stratified by risk. The 70-mg/dl target for individuals with coronary artery disease and diabetes is widely accepted as highly beneficial; simply offering this benefit to all individuals selected for treatment seems reasonable, both because asymptomatic individuals may have life-threatening disease and because the pathogenesis of the disease is identical.

Controlling the Potential Major Expansion in Statin Use

An inevitable outcome of change in the LDL-C initiation and target would be a significant increase in the use of statin drugs. The emergence of pharmacogenetic testing offers a possible solution to overuse. Although one reason for the failure of potent lipid-lowering therapy to markedly reduce cardiac events is the "too little/too late" hypothesis; a second seldom considered reason is that the drugs are ineffective in

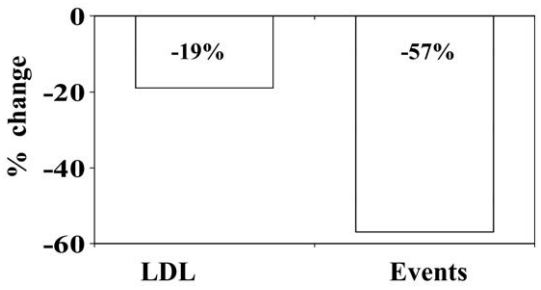

Figure 4 The Effect of a Lifetime of LDL Lowering

The potential impact of a lifetime of lowered LDL-C. In the ARIC (Atherosclerosis Risk in Communities) study, 3% had a *PCSK* mutation at 15-year follow-up. In the ARIC study, 3% or 12,787 subjects had DNA sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) that are associated with reduced plasma levels of low-density lipoprotein (LDL) (12). In the 3,363 black subjects, mutations were associated with a 28% reduction in mean LDL cholesterol and an 88% reduction in the risk of coronary heart disease. In the 9,524 white subjects, a sequence variation in *PCSK9* was associated with a 15% reduction in LDL cholesterol and a 47% reduction in risk. These data suggest that an early and long duration (lifetime) reduction in LDL cholesterol lead to a substantial reduction in coronary events.

as yet unrecognized subsets. Pharmacogenetics suggests that this is highly likely. For instance, one common polymorphism colloquially called KIF-6 (the kinesin-like protein 6 Trg 719 Arg polymorphism) is thought to influence both intracellular transport and endothelial function. In carriers of KIF-6, intensive statin therapy was associated with a 6.8-fold greater reduction in cardiac events than in noncarriers in the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial, despite the same level of on-treatment LDL-C and CRP (13) (Fig. 5). Conversely, noncarriers of the KIF-6 variant, approximately 40% of the U.S. population, experienced virtually no difference in adverse outcomes despite the major differences in on-treatment LDL-C levels between the atorvastatin 80-mg and pravastatin 40-mg treatment groups. Thus, the dose and/or use of statins coincident with altered initiation and target criteria could be tempered by better selection of therapeutic candidates if pharmacogenetic testing can provide insight into those most likely to benefit from therapy (Table 2).

Arguing the Case for and Against Rethinking the Approach to LDL-C Management

There are strong arguments for avoiding these significant changes in the current guidelines (Table 3). The stepwise approach to LDL-C initiation levels and targets is a well-established structure. Guidelines typically are based on randomized clinical trials, whereas the putative normal range of LDL-C is based on inference. For most, however, their principal concern will be uncertainties surrounding toxicity and cost in implementation. Higher drug doses imply an inevitable risk of increased drug toxicity. The risk of long-term aggressive therapy beyond the 5-year clinical trials is unknown, and, by their nature, long-delayed adverse effects are exceptionally difficult to detect. Even with potent agents, a low LDL-C target clearly will not be achievable in many individuals. Younger people may be reluctant to take a drug, creating practical hurdles to implementation. Because lowering initiation levels and targets increases the number of individuals on therapy, the number of individuals not benefiting from therapy must also increase. The impact on health care cost is unpredictable.

Because the principal issue surrounding guideline change is likely to be uncertainty concerning cost and toxicity, the text of new guidelines must completely satisfy this concern by a strong emphasis on a prudent conservative approach to implementation presenting (as do the current guidelines) the target as an desirable option rather than a mandate.

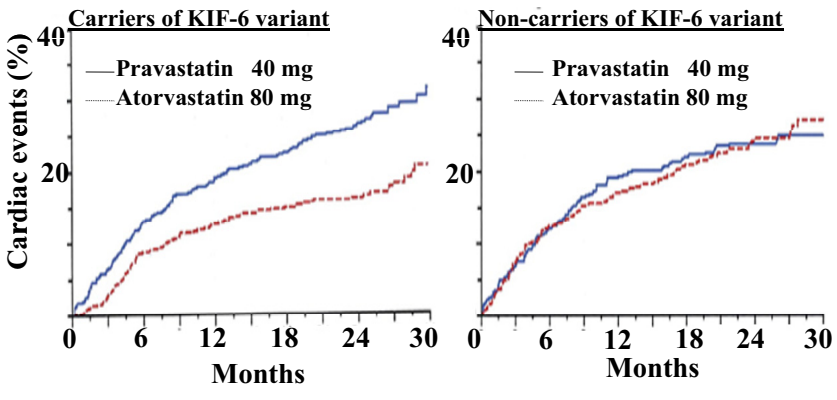

Figure 5 Potential Value of Pharmacogenetics in Patient Selection for Statin Therapy

In the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial, carriers of the KIF6 variant experienced a greater reduction in cardiac events with high-dose atorvastatin than with standard-dose pravastatin **(left)**. In noncarriers, there was no difference in the events with the 2 therapies **(right)**. The number needed to treat with atorvastatin versus pravastatin to prevent 1 event was 10 in KIF6 carriers and 125 in noncarriers. Adapted with permission from Iakoubova et al. (13).

Table 2 Changes in Current LDL-C Guidelines That Could Result in a Major Reduction in Morbidity and Mortality at Acceptable Cost

Criterion	ATP III Guidelines	Proposed
Initiation of treatment	Based on events: absolute 10-yr risk	Based on pathogenesis: relative risk within the individual's age group
Use of a statin	Those who meet risk criteria	Further stratified by genetic capability of response*
Choice of statin	No recommendation	Use a generic drug first in asymptomatic individuals
Target of treatment	Stratified by risk	Putative normal LDL-C range in all treated individuals, in absence of toxicity

*This proposal has a reasonable basis in recent published literature. Because it still requires further validation, it represents a concept, not a specific recommendation.
ATP = Adult Treatment Panel; LDL-C = low-density lipoprotein cholesterol.

Furthermore, such a guideline would include both cautionary data and caveats concerning the tradeoffs among potency, cost, and toxicity of statins, recognizing that these 2 issues will probably outweigh achievement of the target in at least one-fourth of treated patients. Specifically, randomized trials typically report a 3% to 5% myalgia rate, grossly misrepresenting clinical reality by using a run-in period before randomization, then not randomizing those in whom symptoms develop. A further safety consideration is that the current optional <70-mg/dl target should probably have a lower limit, even though there is little information to support any specific value. Because clinical trial data that show no toxicity signal in the lower range are still largely confined to LDL-C levels above 50 mg/dl, a prudent lower limit for LDL-C might be set at 50 mg/dl. Finally, the guidelines would reasonably include a recommendation for the creation of a post-publication database to allow more rigorous analysis of cost, toxicity, and effectiveness.

Given a cautious and conservative approach to each recommendation, the counterbalancing arguments for the proposed changes are also strong (Table 3). A rough estimate of the magnitude of event reduction in the broad population coincident with treatment into the putative normal range can be made from randomized trials. In JUPITER, events in asymptomatic patients were reduced by just less than one-half; in the TNT (Treating to New Targets) trial, events were reduced by approximately one-fourth as LDL-C was further reduced from approximately 100 mg/dl to just above the putative normal range. If roughly similar outcomes were to follow implementation of the proposed guideline changes, then the central argument for change is that it would offer a realistic possibility of dislodging atherosclerotic disease as the leading cause of morbidity and mortality. Although the new guidelines cannot be based on rigorous science, they can have a conceptual foundation that the current guidelines lack. Guidelines represent the best judgment of a group of experts at a point in time. They are not irreversible. Thus, new ATP guidelines, like those with Level of Evidence: A, will have to incorporate medicine's inherent uncertainties and will probably require revision based on subsequent experience. Because guidelines classify data sources, however, no one need be misled about the strength of supporting information. At the practical level, potent generic statins allow the new strategy to be implemented at low individual patient cost. A better distribution of individuals selected for statin therapy probably can be achieved in the near future by the use of pharmacogenetics to predict the magnitude of response to therapy. Finally, long-term preventive therapy for coronary artery disease has a well-established precedent. One may ask whether a low-cost generic statin used in a well-defined at-risk population might provide both more benefit and less risk than aspirin.

LDL-C management recommendations will be developed in a new era in which longer term risk stratification, more objective initiation criteria, a reasonable LDL-C target, and pharmacogenetic stratification are clearly possible. Because the concepts of a putative normal LDL-C and initiation criteria based on pathogenesis rather than first clinical event both incorporate uncertainties, it may be worthwhile to recognize that small incremental change does not alter these uncertainties, but rather serves only to reduce both the risk of adverse outcomes and the potential benefit of therapy. With the vision of dislodging atherosclerotic disease as society's leading cause of dollar expenditure, morbidity, and mortality, a new conceptual foundation for the LDL-C guidelines based on our current knowledge of disease pathogenesis seems to merit very serious consider-

Table 3 Changing the Approach to LDL-C Management: The Pros and Cons

Favoring small incremental change in the current recommendations
Current approach uses a well-established and widely implemented structure.
Guideline changes based on inference are inherently controversial.
A lower LDL-C target will not be achievable in many individuals.
Young asymptomatic individuals may resist preventive therapy.
Expansion of the treated population may increase cost of care.
Use of higher drug doses will increase the incidence of drug toxicity.
The risk of long-term aggressive therapy beyond the 5 years is undefined.
Atherosclerosis is multifactorial, and risk varies widely at the same LDL-C level.
Favoring more substantial change in the current recommendations
Atherosclerosis will likely remain the leading cause of morbidity/mortality with only incremental changes.
Existing guidelines have little conceptual foundation and are viewed by many as outdated.
New guidelines have the conceptual basis of returning LDL-C to normal and initiating therapy earlier in the course of the disease.
Strength of information supporting change can be classified so no one is misled.
Caveats regarding tradeoffs between drug potency, cost, and toxicity can be included.
More aggressive strategy may be implemented at relatively low cost using generic agents.
Pharmacogenetics may control cost by improving distribution of individuals selected for therapy.
Current data suggest proposed changes in initiation and target LDL-C level will result in a major reduction in morbidity and mortality.

LCL-C = low-density lipoprotein cholesterol.

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ation for those facing the daunting task of creating guidelines in an uncertain world.

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Key Words: Adult Treatment Panel III ■ coronary artery disease prevention ■ low-density lipoprotein cholesterol ■ guidelines ■ National Cholesterol Education Program guidelines.